Bandolier 75

What do we think?
What do we know?
What can we prove?

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COX-2 ROUNDUP

This month ***Bandolier*** does something different from the usual trawl of the literature to find high-quality evidence. At the behest of readers, we have chosen to try to make sense of the evidence around the new Cox-2 inhibitors, or coxibs as they are being called.

Problem

This is fundamentally different from finding a systematic review, meta-analysis, or other report that contains golden nuggets of information or mining those nuggets and shaping them into a valuable piece of knowledge. The problem with new interventions is that the amount of information available to the professions or public at large is initially very limited.

Reasons

The reasons for this are obvious. The basic research has to be done, early clinical trials undertaken to demonstrate that the intervention works, larger studies to define doses or routes of administration, and finally large randomised trials to demonstrate efficacy unequivocally, and, to a limited extent, safety. This will be available to registration authorities, but it takes time for papers to be written, peer-reviewed, and published. So new interventions come along without a systematic review of all studies, the type of evidence we increasingly depend upon to make sensible decisions.

Future

It is possible that all the new health technology assessment organisations around the world will provide what we want. But the NICE report will not be available for some months, about a year after Cox-2s first became available in the UK. The ***Bandolier*** approach is to review what is published now, with an updated Internet site as more information becomes available. We'd love to hear from companies when new papers are published, and from readers who see substantive evidence that can help.

In this issue

The beneficial actions of NSAIDs are associated with inhibition of Cox-2 while the harmful adverse effects are associated with inhibition of Cox-1. The claims for coxibs are:

- They are as effective as NSAIDs because they inhibit cyclooygenase-2 enzymes that mediate pain.
- They are not as harmful because they do not inhibit cyclooxygenase-1 enzymes. Inhibition of cyclooxygenase-1 enzymes is responsible for the gastrointestinal ulceration produced by NSAIDs.

It sounds simple, and perhaps may even be simple. But as Oscar Wilde is reported as saying, the pure and simple truth is rarely pure and never simple.

Readers asked ***Bandolier*** to summarise the evidence available on the new Cox-2 analgesics. No mean feat this, because the science extends back more than 10 years, and until very recently the clinical evidence was available only in the form of conference abstracts. But now more substantive reports are available, perhaps the time has come to try.

What follows in this round up of the available evidence ***Bandolier*** could find is by no means a full review of all the evidence. What we have done is to ask companies with coxibs (Cox-2 inhibitors) available or soon to be available for any full publications to supplement our own searching. But it is highly likely that papers will be published in the short time between writing and publication of this issue, and within a few months what is written may be overtaken by much more clinical data.

Still, a start has to be made. We will examine the background to the science of coxibs, followed by examining efficacy in acute and chronic pain, and adverse effects compared with NSAIDs. The two coxibs presently or soon to be available are rofecoxib and celecoxib.

Background science

It seems almost impertinent to try to summarise several decades of scientific endeavour in a few sentences, but perhaps it is a tribute to the science that this is almost possible [1,2]. The cyclooxygenases catalyse the conversion of arachidonic acid to biologically active prostaglandins by cyclooxygenase and peroxidase activity. Active prostaglandins have a diverse variety of physiological functions, including protection of the gastrointestinal tract, renal homeostasis, uterine function, embryo implantation and labour, regulation of the sleep-wake cycle and body temperature.

Cox-1 is predominantly constitutive, and it is found in most tissues, and particularly in platelets, stomach and kidney. The location and pattern of Cox-1 expression indicates that it has responsibility for production of prostaglandins important for responses to circulating hormones and maintenance of gastric mucosal integrity and platelet function. Cox-1 levels can be increased two to four fold by inflammatory stimuli.

Cox-2 is predominantly inducible, though is constitutive in kidney, brain, testicles and tracheal epithelia. Cox-2 is responsible for the biosynthesis of inflammatory prostaglandins. Its levels can increase ten to twenty fold through inflammation, particularly in macrophages, monocytes, synoviocytes, chondrocytes, fibroblasts and endothelial cells.

While the structures of the two enzymes are similar, they differ in a number of ways. Cox-2 is rapidly degraded and has a short half-life. Cox-2 has a larger binding site due to a secondary internal pocket. Compounds binding to this secondary pocket selectively inhibit Cox-2.

Cyclooxygenases and NSAIDs

Conventional NSAIDs inhibit both Cox-1 and Cox-2. This can be demonstrated in a bewildering variety of biological systems. An international consensus meeting [1] has defined Cox-2 specificity and provides a definition of Cox-2 specific inhibitors. It concluded that both rofecoxib and celecoxib fulfil definitions of Cox-2 specificity in man.

Just how more than 40 classical NSAIDs and Cox-2 inhibitors compare in a massively detailed study has been shown, both in the defined assay system and a modified version [2]. From this it is clear that these compounds display a huge range of relative potency for inhibiting Cox-2 relative to Cox-1. Rofecoxib and celecoxib both show very much greater inhibition of Cox-2 than Cox-1.

The problem with all this biochemistry is that it is both fascinating and unhelpful at the same time. As far as ***Bandolier*** can determine, the biological assays can not yet unequivocally predict clinical outcomes. The definition of Cox-2 specificity serves to distinguish between compounds on pharmacological and not clinical grounds. Any benefits for Cox-2 specificity have to be established through randomised trials [1].

Cox-2 inhibition and pain

Upregulation of Cox-2 mRNA and protein occurs in inflammation, has been observed in osteoarthritic cartilage, and results in a great increase in prostaglandin E2 production. Cox-2 has also been observed in synovial tissue in patients with osteoarthritis, but not that of normal patients. Prostaglandin E2 is involved with inflammation, pyresis and hyperalgesia.

Cox-2 is inhibited by classic NSAIDs and by specific Cox-2 inhibitors. This inhibition reduces pain and inflammation.

Cox-1 inhibition and ulcers

The Cox-1 enzyme is constitutive, suggesting that this enzyme synthesises prostaglandins responsible for physiologic housekeeping functions, which include gastrointestinal protection. Classic NSAIDs but not Cox-2 inhibitors inhibit Cox-1 at normal doses. This inhibition reduces the ability of the stomach to protect itself from its acid contents, and the result is a greater propensity to erosion and ulceration. This is a clear oversimplification of a highly complicated process, which includes the ability of NSAIDs to uncouple oxidative phosphorylation in the mitochondria of the mucosa [3,4].

If drugs inhibit Cox-2 but not Cox-1, then the theory would predict that they would be analgesic without the gastrointestinal adverse effects associated with classic NSAIDs. Rofecoxib, for instance, failed to inhibit Cox-1 at doses up to 1000 mg (20- to 80-fold greater than clinical doses) [5].

Cox-2 inhibitors and analgesia

There is a limited published literature on the effectiveness of the new drugs in acute and chronic pain, though many large and high quality studies have been done. Clinical trials take a long time, and getting papers published seems to take almost as long. So while there is a wealth of abstracts, we have few full publications. But we do have the beginnings of an effectiveness literature in acute pain, dysmenorrhoea and osteo- and rheumatoid arthritis.

Acute pain

There are three published reports of coxibs in randomised, double-blind studies in acute pain [5-7]. The results (Table 1) show the coxibs to have analgesic efficacy equivalent to the best analgesics presently available, with numbers needed to treat (NNT) to produce one patient with at least 50% pain relief of 1.9 for rofecoxib 50 mg and 2.8 for celecoxib 200 mg over six hours.

All three studies were in the third molar extraction model, which is as good any other for measuring analgesic efficacy [8]. If there was any difference in these trials from the bulk of studies in the literature, it was that the placebo response rate was somewhat lower, at 7% of patients given placebo having at least 50% pain relief, rather than the overall average of 18% in about 12,000 patients given placebo. But even so, the NNT for ibuprofen 400 mg, used as the active comparator in these three trials, was not significantly different from that from systematic reviews of ibuprofen 400 mg (Table 1).

The analgesic efficacy calculated for Table 1 was over a six-hour period after dosing. This has been the standard time scale because that has been the time over which analgesics traditionally have lasted. For rofecoxib 50 mg the duration of analgesia was much longer than that [6,7]. For instance, at least half, and probably three quarters, of patients given a placebo will be expected to have remedicated by two hours after dose because of unrelieved pain. For ibuprofen in these trials the 50% remedication time was six to nine hours. For

Table 1: Acute pain outcomes with Coxibs and conventional analgesics

Effectiveness of coxibs and analgesics in acute pain models

From Cox-2 trials

Treatment	Number of trials	At least 50% pain relief with		NNT 95% CI
		Placebo	Analgesic	
Rofecoxib 50 mg	3	9/127 (7%)	104/172 (60%)	1.9 (1.6 to 2.2)
Celecoxib 200 mg	1	2/45 (4%)	37/91 (41%)	2.8 (2.1 to 4.4)
Ibuprofen 400 mg	3	9/122 (7%)	65/117 (56%)	2.1 (1.7 to 2.6)

Other analgesics for comparison

Treatment	Number of patients in comparison	At least 50% pain relief with treatment (%)	NNT 95% CI
Paracetamol 1000/Codeine 60 mg	127	62	1.9 (1.5 to 2.6)
Diclofenac 50 mg	636	63	2.3 (2.0 to 2.7)
Ibuprofen 400 mg	2898	53	2.7 (2.5 to 3.0)
Morphine 10 mg IM	946	50	2.9 (2.6 to 3.6)
Paracetamol 1000 mg	2283	45	4.6 (3.9 to 5.4)
Aspirin 600/650 mg	5061	38	4.4 (4.0 to 4.9)
Tramadol 100 mg	882	30	4.8 (3.8 to 6.1)

Data from randomised, double-blind studies in acute pain of initial moderate or severe intensity with pain relief measured over four to six hours

rofecoxib it was about 10 to over 24 hours. More information and better analysis is needed to quantify this, but for duration of analgesia rofecoxib 50 mg may represent a major breakthrough. For celecoxib the same may be true, but it is likely that single doses higher than 200 mg will be needed to achieve this.

Dysmenorrhoea

A randomised, blinded crossover trial compared two regimens of rofecoxib (25 mg initially, followed by 25 mg daily as needed; 50 mg initially, followed by 25 mg daily as needed) with naproxen 550 mg every 12 hours and placebo in 118 women with primary dysmenorrhoea [9]. The three active comparisons were virtually identical in efficacy. Naproxen was identified as being an effective treatment in a previous systematic review [10].

Osteoarthritis

A randomised, double blind study examined the efficacy of rofecoxib 25 mg and 125 mg once daily, or placebo, in a six week study in 219 patients with osteoarthritis of the knee (mean age 64 years) [11]. The two doses of rofecoxib were indistinguishable, but both were significantly better than placebo for analgesic outcomes. It was not possible to compare the outcomes with those from a Cochrane review of osteoarthritis of the knee [12].

There were fewer discontinuations for lack of efficacy with both doses of rofecoxib than for placebo. Adverse effect discontinuations were similar to those seen in osteoarthritis reviews [13]. Two of 73 patients on 25 mg rofecoxib, and five of 74 on 125 mg rofecoxib developed lower extremity oedema, reported as mild except in three at the highest dose (10 times the standard starting dose in osteoarthritis) who discontinued because of the oedema.

A randomised, double blind study examined the efficacy of celecoxib 50 mg, 100 mg and 200 mg twice daily, or placebo, or naproxen 500 mg twice daily in 1003 patients with osteoarthritis of the knee over 12 weeks [14]. Active treatments were better than placebo, and there was some evidence that the lowest dose of celecoxib was less effective. Details of all the quality of life indicators from this trial have been reported separately [15].

There were fewer discontinuations for lack of efficacy with the higher doses of celecoxib than placebo. Adverse effect discontinuations were similar to those seen in osteoarthritis reviews [13]. Peripheral oedema occurred in 1% of patients with place, 2% with naproxen and the lower doses of celecoxib, and 4% on the highest dose of 200 mg twice daily.

Rheumatoid arthritis

Three randomised double blind trials have examined coxibs in rheumatoid arthritis [16-18]. The primary or major outcome was the percentage of patients responding to

Figure 1: Rheumatoid arthritis outcomes with rofecoxib [16]

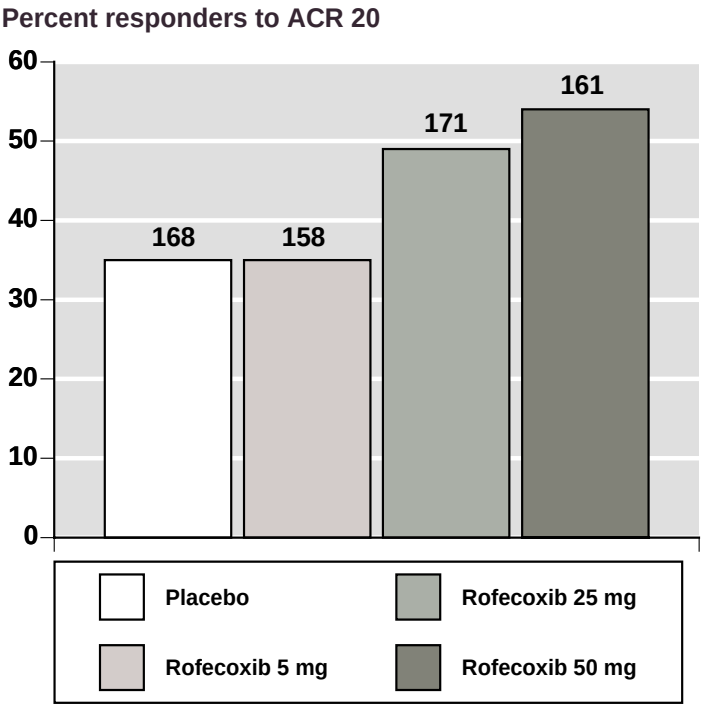
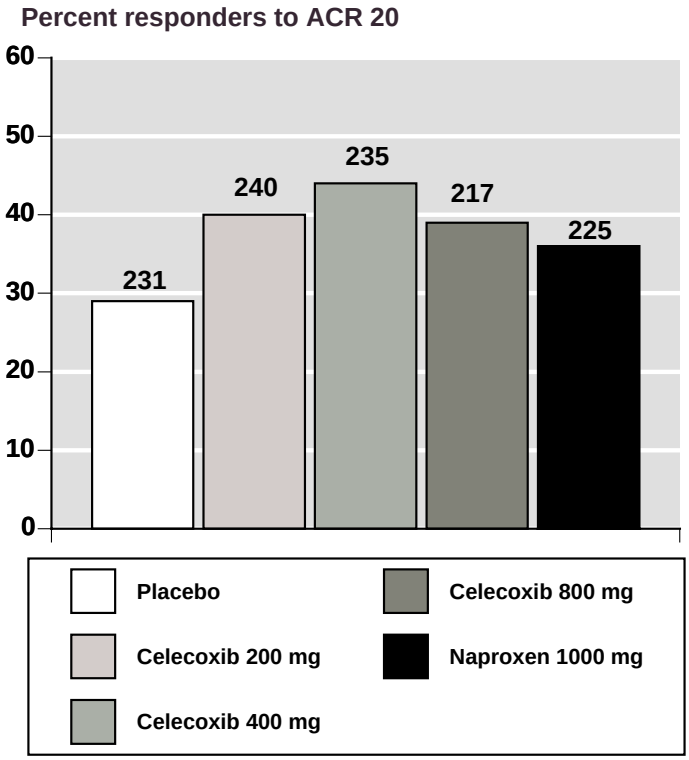


Figure 2: Rheumatoid arthritis outcomes with celecoxib [17]



"American College of Rheumatology 20" criteria. These are a 20% improvement in tender and swollen joint counts and 20% improvement in three of five remaining core measures.

Rofecoxib 25 mg and 50 mg once daily were better than placebo and rofecoxib 5 mg once daily in 658 patients with a mean age of 55 years and mean duration of disease of about 10 years (Figure 1) [16]. Adverse event withdrawals were 3-6% across all treatments, and peripheral oedema was seen in 2.5% of patients on effective doses of rofecoxib.

All three doses of celecoxib (twice daily 100 mg, 200 mg and 400 mg) and twice daily naproxen 500 mg were better than placebo in a 12 week study in 1149 patients with a mean age of 54 years and a mean duration of disease of 11 years (Figure 2) [17]. Adverse event withdrawals were about 5-7% across all treatments, and peripheral oedema was seen in 1-2% of patients on active treatments.

A randomised, double blind and double dummy found no difference in efficacy between celecoxib 200 mg twice daily and diclofenac SR 75 mg twice daily in 655 patients with rheumatoid arthritis over 24 weeks [18]. Adverse effect withdrawals were lower (10%) with celecoxib than with diclofenac (19%), with 6% and 16% respectively being for gastrointestinal adverse effects. Peripheral oedema occurred in 3% of patients on celecoxib and 2% for diclofenac.

Coxibs and endoscopic ulcers

In a randomised double blind study over seven days healthy volunteers were given placebo, or daily doses of 250 mg rofecoxib (10-20 times normal daily dose), 2400 mg ibuprofen or 2600 mg aspirin [19]. Endoscopic examination of the stomach and duodenum was conducted at day seven. Erosion scores showing more than three areas of erosion or an ulcer were low for placebo or rofecoxib, but high for ibuprofen and aspirin (Table 2). One patient on rofecoxib 250 mg developed leg oedema.

Two randomised double blind studies [20, 21] examined endoscopic gastroduodenal ulcers in 1427 patients with osteoarthritis. Patients were randomised to placebo, 25 or 50 mg rofecoxib daily, or 2400 ibuprofen daily for up to six months with active treatment and three months with placebo. The combined results (Figure 3) showed that the cumulative incidence of ulcers of ≥3 mm was no different for placebo or rofecoxib up to three months. At six months the

Table 2: Severe gastric and duodenal erosions in healthy volunteers after one week of treatment

	Placebo	Rofecoxib 250 mg	Ibuprofen 2400 mg	Aspirin 2600 mg
Number	50	49	51	17
Gastric erosions (%)	0	0	37	82
Duodenal erosions (%)	0	6	16	24

More than three erosions or an ulcer (Lanza score 3 or 4 [19])

Figure 3: Endoscopic ulcers with rofecoxib in two randomised trials [20,21]

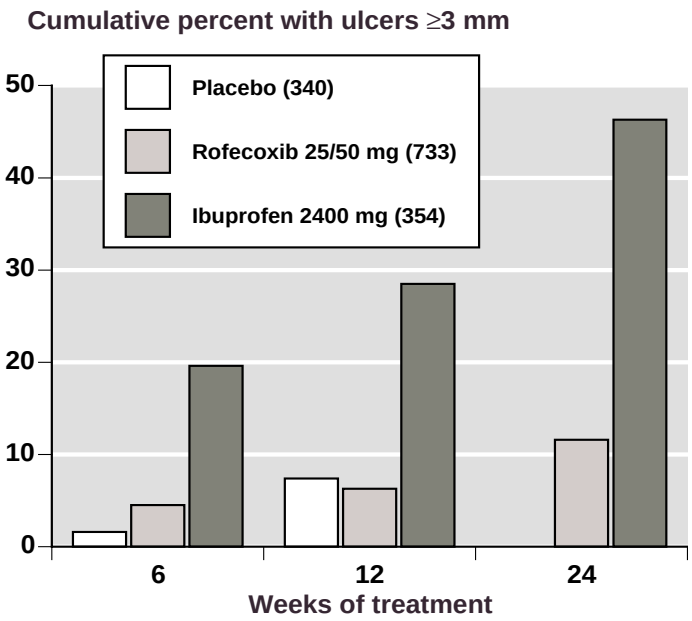
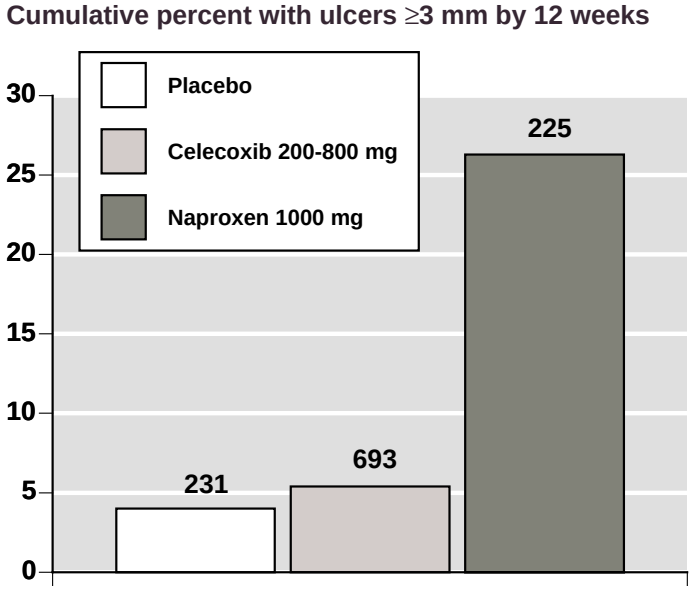


Figure 4: Endoscopic ulcers with celecoxib in a randomised trial [14]



incidence was much higher with ibuprofen (46%) than with rofecoxib (12%), with a number needed to treat of 2.9 (95% CI 2.5 to 3.4) for rofecoxib. This means that for every three patients treated with rofecoxib 25/50 mg daily rather than ibuprofen 2400 mg daily for six months, one endoscopically detected ulcer ≥3 mm would be prevented.

A randomised double blind study in rheumatoid arthritis [20] found no increase in the cumulative incidence of ulcers ≥3 mm by 12 weeks for any dose of celecoxib (200-800 mg daily) compared with placebo (Figure 4). For naproxen 1000 mg daily the incidence was 26%, similar to that found for ibuprofen 2400 mg daily of 28% in osteoarthritis [21].

Another randomised double blind study in rheumatoid arthritis [18] found that 8/190 patients (4.2%) had an ulcer ≥3 mm at endoscopy at 24 weeks with celecoxib 400 mg daily, compared with 29/187 patients (15.5%) with diclofenac SR 150 mg daily (Figure 5).

Combining the data on endoscopic ulcers across the three major trials with 12 week endpoints [17, 20, 21], there was no difference in incidence rate after 12 weeks of treatment between placebo and all doses of coxibs combined with 1156 patients given coxibs (Table 3).

Figure 5: Endoscopic ulcers with clecoxib in a randomised comparison with diclofenac [18]

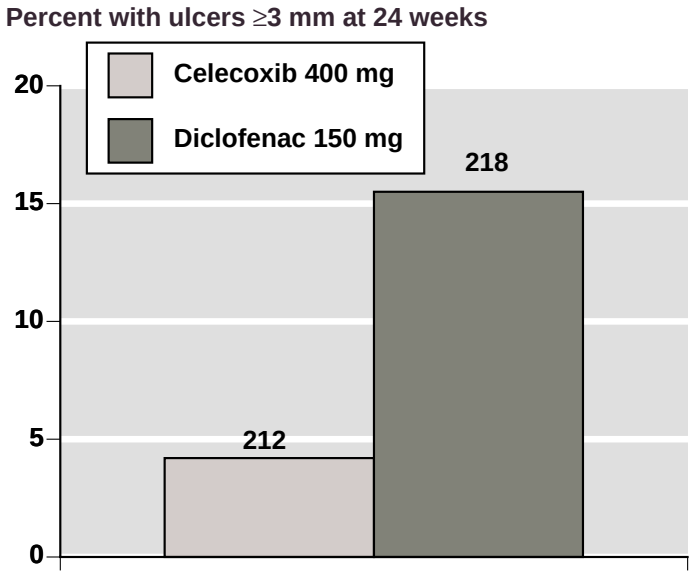


Table 3: Ulcers found by endoscopy in randomised studies of patients with osteo- or rheumatoid arthritis treated for 12 weeks

Treatment	Number of patients	Number with ulcers ≥3 mm	Percent (95% CI)
Placebo	439	29	6.6 (4.3 to 8.9)
Coxib	1156	69	6.0 (4.6 to 7.3)
NSAID	491	137	28 (24 to 32)

All doses of coxibs and different NSAID comparators combined from studies 17, 20 and 21. Outcome is endoscopic ulcer ≥3 mm at 12 weeks.

Table 4: Perforations, ulcers and bleeds in pre-planned analysis of all rofecoxib randomised trials [22]

Treatment	Number of patients	Exposure (patient years)	Number with PUB	Mean exposure (years)	Crude risk (%)	Percent per 100 patient years ove	
						4 months	12 months
Placebo	514	112	3	0.22	0.58	2.7	
Rofecoxib	3357	1428	19	0.43	0.57	2.5	1.3
NSAID	1564	615	16	0.39	1.02	7.2	2.6

Coxibs and gastrointestinal bleeding

A pre-planned meta-analysis of perforations, ulcers and bleeds (PUBs) in the phase II/III randomised trials of rofecoxib examined serious gastrointestinal bleeding [22]. A blinded external adjudication committee assessed PUBs. The prespecified criteria were stringent. Perforation or ulcer had to be confirmed by endoscopy, surgery, radiography or autopsy. Clinically significant upper gastrointestinal bleeding was frank haematemesis, frank melaena, haem positive stool and documented upper gastrointestinal lesion or bleeding documented by endoscopy or angiography.

There were 5435 patients in the analysis. The mean age was 63 years (range 38 to 94 years), with 45% over 65 years. Ten percent had a previous medical history of PUB.

Patients were only given placebo for four months. Over four months, the rates of PUB per 100 patient years were identical for rofecoxib (mean dose 25 mg) and placebo, with a relative risk of 0.94 (95% CI 0.25 to 3.6) (Table 4). The cumulative incidence of PUBs over 12 months with rofecoxib was about half that with classic NSAIDs, with a relative risk of 0.51 (0.26 to 1.0).

In this analysis a weakness was that patients who developed an endoscopic ulcer in the original trials discontinued treatment. Since NSAIDs produced much higher rates of endoscopic ulcer than did placebo or rofecoxib, the likelihood was that results of the pooled analysis were biased against rofecoxib because patients with endoscopic ulcer were more likely to develop a perforation, ulcer or bleed.

Comment

So where does all this information leave us? Several editorials or reviews [23-25] conclude that Cox-2 inhibitors represent an advance, but the issue is the eventual place of Cox-2 inhibitors in practice. Although the amount of efficacy information remains limited, the major questions are not about efficacy. For efficacy in acute and chronic pain the coxibs seem to be a match for classical NSAIDs.

It is the reduced potential for harm, and particularly serious gastrointestinal bleeding where the added value lies. The evidence so far looks good. Coxibs do not produce the endoscopic ulcers found with NSAIDs, and the balance of evidence is that serious bleeding is no more frequent than with placebo. The caveat is that the amount of information on which to base this latter observation is very limited (38 PUBs).

The evidence for harm from classic NSAIDs continues to mount [26-28]. In the USA, NSAIDs cause more deaths than multiple myeloma, asthma, cervical cancer and Hodgkin's disease, and about as many as HIV/AIDS [26]. On average 1 in 1200 patients taking NSAIDs for at least two months will die from gastroduodenal complications who would not have died if they had not taken NSAIDs [28]. Prophylactic use of acid suppression has its problems [27], including lack of efficacy of histamine antagonists. Proton pump inhibitors and misoprostol are effective, but are expensive and have their own problems. Much of the evidence for harm from NSAIDs has been rehearsed in ***Bandolier*** before, and the evidence is summarised on our pain Internet site [29].

Table 5: Risk of NSAID-related gastrointestinal bleeding or death by age

Age range (years)	Number taking NSAID	Number with GI bleed	Chance of GI bleed due to NSAID	Chance of dying from GI bleed due to NSAI
			Risk in any one year is 1 in:	
16-45	2100	1	2100	12353
45-64	3230	5	646	3800
65-74	2280	4	570	3353
≥75	1540	14	110	647

Data from reference 30, recalculated for a PCG of 100,000 people

It will all come down to cost and risk, of course. The authors of a JAMA editorial [24] have estimated that for low risk patients in whom the risk of developing an NSAID related ulcer complication is 0.4% the cost of preventing a single complication is $400,000. Where the risk is higher, as in elderly patients over 75 years or with a prior history with a 5% risk the cost is much, much, less at $30,000, and probably most or all of that cost would be offset by costs of coprescribed acid suppressants. Several health technology assessments of the cost-effectiveness on Cox-2 inhibitors are promised for 2000.

But it may be the risk aspect that eventually becomes the driver. Table 5 shows the annual risks of NSAID-related gastrointestinal bleed, and death from a gastrointestinal bleed, from a large population in England [30]. Clearly the risks increase with age. The risk of dying from a road traffic accident in England in any one year is 1 in 17,000 or so, which ***Bandolier*** finds a useful base for comparison, as almost all of us find that level of risk acceptable as individuals (otherwise there wouldn't be so much traffic), but unacceptable as a society (we keep trying to reduce road accident deaths). If we believe that NSAID-related ulcers are precursors of more serious events, then knowing which patients have ulcers might be helpful. A new faecal test for calprotectin [31] offers at least the possibility of this.

Coxibs and renal function

Cox-2 is found in the kidney and it is inhibited both by classic NSAIDs and by Cox-2 specific inhibitors. This inhibition is probably responsible, at least in part, for the occasional cases of peripheral oedema seen in the clinical trials. A meta-analysis of the effect of NSAIDs on postoperative renal function [32] reports a clinically unimportant transient reduction in renal function with NSAIDs in this circumstance. A randomised comparison of rofecoxib and indomethacin suggested that rofecoxib caused clinically insignificant and transient retention of sodium, but no depression of glomerular filtration rate [33].

Clinical practice is not the same as clinical trials, from which patients with more severe disease or with multiple comorbidities may be excluded. It is likely that coxibs will be used on patients for whom a classic NSAID was contraindicated because of other problems. Prudence would suggest mentioning the possibility of oedema, and keeping a watching brief on kidney function.

Coxibs – the future

There are two other areas where coxibs may have a role in the future, though for both these are very early days and we have very limited evidence, if any.

The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) has recently reviewed the evidence for NSAIDs and Cox-2 inhibitors in prevention or treatment of colorectal cancer [34]. This is a useful review on cyclooxygenase inhibition and colorectal cancer, and it reminds us that we still lack any really good evidence, and any effect of NSAIDs may not be related to cyclooxygenase inhibition.

That there may be a relationship between Cox-2 expression and colorectal cancer is another matter. A preliminary study from Ireland [35] suggests that Cox-2 expression may be related to survival in patients with colorectal cancer. In 76 patients with colorectal cancer, the five-year survival in those with no Cox-2 staining from samples taken at surgery was 92%. In those in whom the Cox-2 staining was apparent the median five-year survival was 41%. But Cox-2 staining was related to more advanced cancer and greater lymph node involvement, so it is unlikely to be an independent mechanism. It may be a co-incidental finding.

Lack of definitive diagnostic criteria and significant randomised trials handicap the evidence that NSAIDs have a role in preventing the progression of, or protection against Alzheimer's disease [36]. There is some evidence for the involvement of cyclooxygenase-2.

In both these areas, Alzheimer's and colorectal cancer, large randomised trials are under way.

And finally

A reminder that Cox-2 inhibitors have no effect on platelet aggregation, and will not substitute for aspirin in this indication.

As more information on Cox-2 inhibitors becomes available, it will be summarised on the ***Bandolier*** Internet site, and in these pages as well if appropriate.

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